Cell-virus kinetics

Healthy CD4⁺ T cell in the blood

$$\frac{dH_B(t)}{dt} = \lambda_H(t) + \sigma_{LB}H_L(t) - \sigma_{BL}H_B(t)(1+\gamma I) - \mu_H H_B(t)$$

(1) Inflow of new CD4⁺ T cell from the thymus; (2) inflow of CD4⁺ T cell from the lymphatic system; (3) outflow of CD4⁺ T cell into the lymphatic system; (4) natural death of CD4⁺ T cell.

Healthy CD4+ T cell in the lymphatic system

$$\frac{dH_L(t)}{dt} = r(t)H_L(t) + \sigma_{BL}H_B(t)(1+\gamma I) - \sigma_{LB}H_L(t) - \mu_H H_L(t) - kH_L(t)V_L(t)$$

(1) New cells from homeostatic CD4⁺ T cell proliferation; (2) CD4⁺ T cell entering cell cycle; (3) inflow of CD4⁺ T cell from the circulation; (4) outflow of CD4⁺ T cell into the circulation; (5) natural death of CD4⁺ T cell; (6) infection by HIV; (7) reversion of abortively-infected CD4⁺ T cell.

Abortively-infected CD4⁺ T cell

$$\frac{dH_a(t)}{dt} = fkH_L(t)V_L(t) - \mu_a H_a(t)$$

(1) Infected cells that are non-permissive; (2) reversion of abortively-infected CD4⁺ T cell; (3) abortively-infected CD4⁺ T cell undergoing pyroptosis.

Inflammatory cytokine (IL-1β)

$$\frac{dI(t)}{dt} = N_I\mu_a H_a(t) - \mu_I I(t)$$

(1) Interleukin released from abortively-infected CD4⁺ T cell undergoing pyroptosis; (2) interleukin decay.

Productively-infected CD4⁺ T cell

$$\frac{dH_p(t)}{dt} = (1-f)kH_L(t)V_L(t) + \alpha H_l(t) - \alpha' H_p(t) - \left(\mu_p + \beta C_e(t)\right)H_p(t)$$

(1) Infected cells that are permissive; (2) cells coming out of latency; (3) cells going into latency; (4) natural death and cytotoxic T cell killing of productively-infected CD4⁺ T cell.

Latently-infected CD4⁺ T cell

$$\frac{dH_l(t)}{dt} = \alpha' H_p(t) - \alpha H_l(t) - \big(\mu_l + \beta C_e(t)\big)H_l(t)$$

(1) Cells going into latency; (2) cells coming out of latency; (3) natural death and cytotoxic T cell killing of latently-infected CD4⁺ T cell.

HIV particles in the lymphatic system

$$\frac{dV_L(t)}{dt} = N_V H_p(t) + D_{BL}\big(V_B(t) - V_L(t)\big) - \mu_V V_L(t)$$

(1) New particles released from productively-infected CD4⁺ T cell; (2) exchange of particles with the circulation; (3) HIV particle decay.

HIV particles in the circulation

$$\frac{dV_B(t)}{dt} = D_{LB}\big(V_L(t) - V_B(t)\big) - \mu_V V_B(t)$$

(1) Exchange of particles with the lymphatic system; (2) HIV particle decay.

Naïve CD8⁺ T cell

$$\frac{dC_n(t)}{dt} = -\varepsilon C_n(t) A_m(t) \left(\frac{E_s(t)}{E_s(t) + \phi}\right)\left(\frac{H_L(t)}{H_L(t) + \eta}\right)$$

(1) Inflow of new CD8⁺ T cell from the thymus; (2) naïve CD8⁺ T cell activation; (3) natural death of naïve CD8⁺ T cell.

Effector CD8⁺ T cell

$$\frac{dC_e(t)}{dt} = \varepsilon C_n(t) A_m(t) \left(\frac{E_s(t)}{E_s(t) + \phi}\right)\left(\frac{H_L(t)}{H_L(t) + \eta}\right) + \varepsilon C_m(t) V_L(t) + \rho C_e(t) - \omega C_e(t) - \mu_e C_e(t)$$

(1) Naïve CD8⁺ T cell activation; (2) memory CD8⁺ T cell reactivation; (3) effector CD8⁺ T cell proliferation; (4) memory CD8⁺ T cell formation; (5) natural death of effector CD8⁺ T cell.

Memory CD8⁺ T cell

$$\frac{dC_m(t)}{dt} = \omega C_e(t) - \varepsilon C_m(t) V_L(t)$$

(1) Memory CD8⁺ T cell formation; (2) memory CD8⁺ T cell reactivation.

Antigen presentation

Antigenic protein in the interstitial fluid

$$\frac{dP_e(t)}{dt} = c_1 N_P \mu_V V_B(t) - A_i(0) \upsilon_P P_e(t)$$

(1) Antigenic protein released from decaying HIV particle in the circulation; (2) antigenic protein uptake by antigen-presenting cells.

Antigenic protein in the endosome

$$\frac{dP_i(t)}{dt} = c_2 \upsilon_P P_e(t) - \mu_P P_i(t)$$

(1) Antigenic protein uptake by antigen-presenting cells; (2) degradation of antigenic proteins into short peptides.

Short peptide in the endosome

$$\frac{dS(t)}{dt} = \mu_P P_i(t) + \delta E_i(t) - \delta' S(t) M_i(t) - \mu_S S(t)$$

(1) Short peptides released from degrading antigenic protein; (2) short peptides released from MHC-peptide dissociation; (3) peptide association with MHC; (4) degradation of short peptides.

MHC-peptide complex in the endosome

$$\frac{dE_i(t)}{dt} = \delta' S(t) M_i(t) - \delta E_i(t) - \mu_E E_i(t) - \pi E_i(t)$$

(1) Peptide association with MHC; (2) MHC-peptide dissociation; (3) degradation of MHC-peptide complex; (4) exocytosis of MHC-peptide complex.

MHC-peptide complex on the cell surface

$$\frac{dE_s(t)}{dt} = c_3 \pi E_i(t) - \delta E_s(t)$$

(1) Exocytosis of MHC-peptide complex; (2) MHC-peptide dissociation.

MHC molecule on the cell surface

$$\frac{dM_s(t)}{dt} = \delta E_s(t) - \upsilon_M M_s(t)$$

(1) Dissociation of MHC-peptide complex on the cell surface; (2) endocytosis of MHC molecule on the cell surface.

MHC molecule in the endosome

$$\frac{dM_i(t)}{dt} = \lambda_M + \frac{1}{c_3}\upsilon_M M_s(t) + \delta E_i(t) - \delta' S(t) M_i(t) - \mu_M M_i(t)$$

(1) Synthesis of new MHC molecule; (2) endocytosis of MHC molecule on the cell surface; (3) MHC-peptide dissociation; (4) MHC association with peptide; (5) degradation of MHC molecule.

Parameters

CD4+ T cell homeostasis

There are 2.2×10^{11} CD4+ T cells in the lymphatic system of a healthy person and 4.9×10^{9} cells in the circulation, corresponding to 2% of the total CD4+ T cells in the body in the circulation at all times. For simplicity, let $H_B(0) = 10^3$ cells μL^{-1} (circulation volume $= 5 \times 10^6$ μL) and $H_L(0) = 2 \times 10^{11}$ cells. At any given time, a fraction of 4% of CD4+ T cells in a healthy person's body undergo apoptosis. Therefore, $\mu_H = 0.004$ day^{-1}. As for the inflow of new CD4+ T cells, there are two sources: thymocyte differentiation and homeostatic CD4+ T cell proliferation. For simplicity, we assume that thymocyte differentiation only maintains the cell population in the circulation while homeostatic proliferation only maintains that in the lymphatic system. As Bajaria *et al.* did, we formulated the inflow of new CD4+ T cells from the thymus, accounting for thymic involution, as

$$\lambda_H(t) = \mu_H H_B(t) \times 0.97^{t/365}$$

As for the rate of CD4+ T cell proliferation, we formulated it as

$$r(t) = r_{max}\left(1 - {H_{tot}(t)}/{H_{max}}\right)$$

This formula reflects the density-dependent nature of homeostatic proliferation and should capture the increase in CD4+ T cell proliferation typically observed in a progressing HIV infection. Since the daily natural death rate of CD4+ T cell is 4%, we assume that $r(0) = 0.004$ day^{-1}. We chose $r_{max} = 0.055$ day^{-1} as did Hapuarachchi *et al.* As $H_{tot}(0) = H_L(0) = 2 \times 10^{11}$ cells, we chose $H_{max} = 2.15686 \times 10^{11}$ cells. According to Abbas *et al.*, 2.5×10^{10} CD4+ T cells circulate from the lymphatic system to the circulation and vice versa each day. Therefore, we calculated the rate of CD4+ T cell transfer from the lymph to the blood to be

$$\sigma_{LB} = \frac{2.5 \times 10^{10}}{H_L(0) \times \text{circulation volume}}\,\text{day}^{-1} = 2.5 \times 10^{-8}\,\text{day}^{-1}$$

Similarly, the rate of transfer from the blood to the lymph is

$$\sigma_{BL} = \frac{2.5 \times 10^{10} \times \text{circulation volume}}{H_B(0)} \text{day}^{-1} = 1.25 \times 10^{14}\ \text{day}^{-1}$$

HIV kinetics

Parameter	Value	Reference
k	2.4×10^{-5} μL molecule^{-1} day^{-1}	Wang *et al.*, Peeyush Chandra (presentation), Tendai Mugwagwa (essay)
f	0.95	Wang *et al.*
μ_a	0.001 day^{-1}	Wang *et al.*
N_I	15 molecules	Wang *et al.*
μ_I	6.6 day^{-1}	Wang *et al.*
γ	4×10^{-6} μL molecule^{-1}	Wang *et al.*
α	0.03 day^{-1}	Bajaria *et al.*
α'	0.01 day^{-1}	Bajaria *et al.*
μ_p	0.5 day^{-1}	Bajaria *et al.*
μ_l	0.000525 day^{-1}	Bajaria *et al.*
N_V	2000 molecules cell^{-1} day^{-1}	Wang *et al.*
μ_V	23 day^{-1}	Wang *et al.*
D_{LB}	2×10^{-8} day^{-1}	See text
D_{BL}	10^6 day^{-1}	See text

The values for viral particle exchange rates between the circulation and the lymphatic system are derived from Wang *et al.*

$$D_{LB} = \frac{0.1\ \text{day}^{-1}}{\text{circulation volume}} = 2 \times 10^{-8}\ \text{day}^{-1}$$

$$D_{BL} = 0.2\ \text{day}^{-1} \times \text{circulation volume} = 10^6\ \text{day}^{-1}$$

CD8⁺ T cell response

Parameter	Value	Reference
β	10 μL cell^{-1} day^{-1}	Wang *et al.*
ε		
η	10^{11} cells	See text
ρ	2.9 day^{-1}	de Boer *et al.*
ω	0.009 day^{-1}	de Boer *et al.*
μ_e	0.57 day^{-1}	de Boer *et al.*

The value for density of CD4⁺ T cell required to achieve half of the maximal naïve CD8⁺ T cell activation rate used in Wang *et al.* one-compartment model is 500 cells μL^{-1}. Because our model relates naïve CD8⁺ T cell activation not to the density of CD4⁺ T cell in the circulation (which is the assumption in Wang *et al.*) but to the number of CD4⁺ T cell in the lymphatic system where naïve T cell activation occurs, we set our parameter at a value that is of the same proportion to the initial number of CD4⁺ T cell in the lymphatic system as that of the parameter used in Wang *et al.* to the initial CD4⁺ count.

Antigen presentation

Parameter	Value	Reference
N_P	5000 molecules	Briggs *et al.*
υ_P	14.4 day^{-1}	Chen *et al.*
μ_P	17.28 day^{-1}	Chen *et al.*
δ	5.20128 day^{-1} to 5.20128 × 10^9 molecules μL^{-1} day^{-1}	See text
δ'	5.20128×10^3 molecules μL^{-1} day^{-1}	Chen *et al.*
μ_S	144 day^{-1}	Chen *et al.*
μ_E	0.1663 day^{-1}	Chen *et al.*
π	28.8 day^{-1}	Chen *et al.*
υ_M	14.4 day^{-1}	Chen *et al.*
ϕ	0.19048 molecules μm^{-2}	See text
λ_M	3.118125×10^{14} molecules μL^{-1} day^{-1}	See text
μ_M	1.663 day^{-1}	Chen *et al.*

The value for MHC-peptide complex dissociation rate constant was varied during the simulation based on the known range of MHC-peptide complex dissociation constant (10^{-3} to 10^6). The coefficient c_1 relates the flow of antigenic proteins released from decaying viral particles in the circulation to the change in the concentration of antigenic proteins available for uptake by antigen-presenting cells, which we assume reside in the interstitial fluid compartment. Therefore,

$$c_1 = \frac{\text{circulation volume}}{\text{interstitial fluid volume}} = \frac{5 \times 10^6\ \mu\text{L}}{11 \times 10^6\ \mu\text{L}} = 0.45455$$

The coefficient c_2 relates the uptake of antigenic protein by an antigen-presenting cell in the interstitial fluid compartment to the change in the concentration of antigenic proteins in its endosomal compartment. Therefore,

$$c_2 = \frac{\text{interstitial fluid volume}}{\text{endosomal compartment volume of one cell}} = \frac{11 \times 10^6\ \mu\text{L}}{4 \times 10^{-10}\ \mu\text{L}} = 2.75 \times 10^{16}$$

The coefficient c_3 relates the exocytosis of MHC-peptide complex from the endosomal compartment to the cell surface. Therefore,

$$c_3 = \frac{\text{endosomal compartment volume}}{\text{antigen-presenting cell surface area}} = \frac{4 \times 10^{-10}\ \mu\text{L}}{2100\ \mu\text{m}^2} = 1.9047619 \times 10^{-13}\ \frac{\mu\text{L}}{\mu\text{m}^2}$$

According to Chen *et al.* the number of MHC-peptide complex required to achieve half of the maximal naïve T cell activation rate is 400, but the parameter is dimensionless. We assume that the value is for one antigen-presenting cell, so we divided that by the surface area of an antigen-presenting cell to obtain 0.19048 units of MHC-peptide complex per μm^2 of antigen-presenting cell surface.